REMARKS

Claim Amendments

Claims 1, 3-12, 14-20, 22-23, 25-27 and 31-32 are pending. Claims 2, 13, 21, 24 and 28-30 have been previously cancelled. Claims 1, 3-8, 12, 19, 20, 22, 23 and 25-27 are allowed. Claim 15 is amended. Support for amended claim 15 may be found at page 20, lines 8 to 11 of the specification. The amendments are being made solely to advance prosecution of this application to allowance and do not constitute an acquiescence, abandonment or disclaimer with respect to a subject matter originally claimed. Applicants reserve the right to pursue any excluded subject matter by way of one or more further application(s).

Claim Rejections – 35 USC §112

The Examiner has maintained the rejection of claims 9, 14-19, and 31 under 35 USC §112, first paragraph, as the specification allegedly fails to reasonably provide enablement for compositions for or methods of treatment *in vivo*. Applicants respectfully traverse the rejection.

At the priority date, LL-37 had been demonstrated in the art to be successfully delivered *in vivo* either by injection of the peptide or by delivery of a nucleic acid encoding LL-37 such that the LL-37 retains its biological activities against infection.

The Examiner states that he has considered the Applicants' arguments in light of the cited references, but does not find them persuasive. However, the Examiner appears to be referring to Bals *et al.*, "Transfer of a Cathelicidin Peptide Antibiotic Gene Restores Bacterial Killing in a Cystic Fibrosis Xenograft Model", *J. Clin. Invest.*, 103(8):1113-1117, (April 1999) cited in the IDS annexed to the Office Action mailed 9 April 2007 as AY4, whilst the Applicants' arguments related to Bals *et al.*, "Augmentation of Innate Host Defense by Expression of a Cathelicidin Antimicrobial Peptide", *Infection and Immunity*, (67)11:6084-6089 (November 1999) cited in the IDS annexed to the Office Action dated 9 April 2007 as AS2. The confusion between the documents appears to have arisen from the Applicants incorrectly referring to Bals *et al.*, "Augmentation of Innate Host Defense by Expression of a Cathelicidin Antimicrobial Peptide", *Infection and Immunity, (67)11:6084-6089* (November 1999) as AY4 in the response filed on 28 March 2008 and the Applicants apologize for this error.

Bals *et al.* "Augmentation of Innate Host Defense by Expression of a Cathelicidin Antimicrobial Peptide", *Infection and Immunity, (67)11:6084-6089* (November 1999) reports the results of a study analyzing the impact of overexpression of a naturally occurring human antimicrobial cathelicidin peptide (LL-37/hCAP-18) in murine models of infection and sepsis (see Bals *et al.*, page 6084, right column, second paragraph). This document thus relates to the activity of LL-37 *in vivo*.

Bals *et al.* investigates the functional consequences of LL-37/hCAP-18 overexpression in mouse airways by challenging mice given an intratracheal injection of recombinant adenovirus vectors carrying the cDNA for LL-37/hCAP-18 with a sub-lethal dose of *P. aeruginosa*. Bals *et al.* teaches that, compared to control animals, mice expressing LL-37/hCAP-18 had a significantly smaller number of bacteria in their lungs (see page 6086, right column, lines 1 to 5 and page 6087, left column, lines 9 to 15 of Bals *et al.*).

Bals *et al.* also discloses the intravenous administration of the adenovirus vector coding for LL-37/hCAP-18 and reports that this resulted in an acute rise in the concentration of LL-37 peptide in serum, that the LL-37 peptide was still present 83 days after injection. Bals *et al.* also demonstrates that the LL-37 peptide has a half-life of approximately 3.4 days following intravenous injection of purified peptide (see page 6087, left column, lines 16 to 28 of *Bals et al.*).

The mice expressing LL-37 from the adenovirus vector were injected with *E. coli* CP9 5 days after vector administration and monitored for mortality. Control animals experienced 90 to 100% mortality within 24 hours while mortality was decreased to 15 to 25% in animals that received LL-37/hCAP-18 vectors. Bals *et al.* concludes that there is a clear relationship between the dose of vector, the LL-37 concentration in serum and improved survival (see page 6087, right column, lines 13 to 22). Bals *et al.* also refers to an earlier study showing that intravenous or intraperitoneal injection of various forms of LL-37/hCAP-18 peptides also protects animals against septic death (see page 6087, right column, lines 9 to 13).

In the concluding paragraphs of Bals *et al.* it is stated that "*the data presented in this study support the notion that expression of a mammalian antimicrobial peptide in a different species provides protection against bacterial pathogens*" and that "*overexpression of antimicrobial substances by means of gene transfer or upregulation of gene expression with*

inducers may be a feasible way to treat infection and endotoxemia" (see page 6088, right column, third and fourth paragraphs).

Thus, the prior art teaches that LL-37 administered to animals has anti-microbial effects *in vivo*. The instant specification teaches that some individuals have increased susceptibility to infection because they have lower than normal levels of LL-37 and that administration of LL-37 to such patients reduces their susceptibility to infection. The instant specification provides enablement for such methods in view of the demonstration in the prior art that LL-37 maintains its anti-microbial activity *in vivo*.

Reconsideration and withdrawal of the rejection of claims 9, 14-19 and 31 made under the first paragraph of 35 USC §112 are requested because the specification enables a person skilled in the art to which it pertains, or in which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

The Examiner has rejected claims 10, 11 and 32 under 35 USC §112, first paragraph, because the specification, while being enabling for methods for the determination of levels of LL-37 in body fluids and *in vitro* methods for bactericidal assays utilizing LL-37, allegedly does not reasonably provide enablement for compositions for or methods of treatment *in vivo*. Applicants respectfully traverse the rejection.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (i) the nature of the invention, (ii) the state of the prior art, (iii) the predictability or lack thereof in the art, (iv) the amount of direction or guidance present, (v) the presence or absence of working Examples, (vi) the quantity of experimentation necessary, (vii) the relative skill of those in the art, and (viii) the breadth of the claims.

The Examiner has commented on the nature of the invention, the state of the prior art, the predictability in the art and the amount of direction or guidance present in the specification and has concluded that the extremely broad treatment scope of the instant claims constitutes merely an invitation to experiment without a reasonable expectation of success. Applicants respectfully disagree.

The nature of the invention – claims 10 and 11 are drawn to a two-step method. Step 1 is determining a level of LL-37 in a subject and identifying whether the subject has an increased susceptibility to infection by determining whether the level of LL-37 is lowered compared to the level of LL-37 in a control sample from a normal subject. Step 2 is the treatment of the subject to reduce the risk of infection by administering an antimicrobial agent.

Claim 10 does not require a specific antimicrobial agent. Many different antimicrobial agents are known in the art and it would be within the ordinary skill of a person skilled in the art to administer a known antimicrobial agent to the subject. For example, the protegrin peptide, IB-367 disclosed in Mosca *et al.* could be used and there are many other such antimicrobial agents having antibacterial activity that could also be administered (Reference AY6 cited in the IDS of March 28, 2008). Accordingly, a person skilled in the art would be able to make and use the invention commensurate in scope with claim 10.

Claim 11 requires that the antimicrobial agent is LL-37. Claim 32 is drawn to a method of treating an infection in a subject receiving or who has received a cytostatic drug, corticosteroid or growth factor, wherein the subject has a lowered level of LL-37 compared to a normal subject. Claims 11 and 32 are thus both drawn to methods of treating an infection in a defined group of subjects, i.e. subjects who have an increased susceptibility to infection as a result of their having a lowered level of LL-37, by administering LL-37 to the subjects.

The state of the prior art – as acknowledged by the Examiner, the prior art teaches that LL-37 is an antimicrobial peptide found in human neutrophils and expressed in skin and gingiva and appears to play an important role in defense against invading pathogens (Weinberg *et al.*, 1998) (Reference AS cited in the IDS of April 7, 2005). Also, at the time of filing of the instant application, the art provided experimental *in vivo* information concerning treatment of infection of LL-37 in subjects (Bals *et al.*, November 1999 – see above analysis). Thus, it is predictable from the prior art that administration of LL-37 to subjects may be used to treat or prevent infection.

The amount of direction or guidance present – as acknowledged by the Examiner, the specification teaches methods for the determination of levels of LL-37 in body fluids and *in vitro* methods for bactericidal assays utilizing LL-37. The specification is also sufficient for the scope of the instant claims, i.e., *in vivo* treatment of infections or prophylactic treatment of subjects

having an increased susceptibility to infection by virtue of them having a lowered level of LL-37, by administering LL-37 to the subjects. In particular, suitable compositions and dosage levels are disclosed in the instant specification at page 19, line 30 to page 22, line 2. Further guidance is available from the prior art. For example, Bals *et al.*, November 1999 discloses pharmacokinetic data for the LL-37 peptide (see page 6085, right column, lines 9 to 13 and page 6087, left column, lines 16 to 28).

Furthermore, the *in vivo* antimicrobial effect of LL-37 in neutropenic mice has subsequently been demonstrated. In Cirioni *et al.*, Shock, 30(4):443-448 (2008) (a copy of which is being cited and provided with the accompanying SIDS) reports that mice were rendered neutropenic by administering cyclophosphamide on days -4 and -2 preinfection and that septic shock was induced at time 0 by injecting *P. aeruginosa*. Some mice were then treated with 1mg/kg of LL-37 (which corresponds to a dose specified in the instant specification at page 21, lines 11 to 12). Administration of 1mg/kg of LL-37 was significantly superior to the control at reducing the mouse lethality rate and bacterial burden in organs (see Abstract, lines 5 to 11, page 445, left column, last four lines to right column, line 8, page 446, right column, last three lines to page 447, left column, first four paragraphs). Cironi *et al.* therefore provides evidence that the teaching of the present specification enables a skilled person to carry out the claimed treatment methods.

Thus, the specification enables a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. In view of the *in vivo* data provided in the prior art, the skilled person would have no reason to doubt that the methods of treatment taught in the instant specification would be successful.

Reconsideration and withdrawal of the rejection of claims 10, 11 and 32 made under the first paragraph of 35 USC §112 are requested because the specification enables a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

Information Disclosure Statement

An Information Disclosure Statement (IDS) was filed on April 7, 2005. The Examiner crossed out references AM, AO, AP, presumably because the translation check box indicated

"no". However, submission of these references was in compliance with the requirements under 37 C.F.R. §1.98(a)(3) because these references were cited in a Search Report and a copy of the Search Report was provided with the IDS that was filed on April 7, 2005. Reconsideration and entry of these references into the record are respectfully requested.

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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